MODULATORS OF TRYPTOPHAN CATABOLISM

FIELD OF THE INVENTION

[0001] The present invention relates to compounds that are modulators of tryptophan (Trp) catabolism, and their use in the treatment of diseases and/or conditions associated with the abnormal or elevated catabolism of tryptophan.

[0002] In particular, compounds of the invention are modulators of tryptophan catabolism. The present invention also relates to methods for the preparation of the compounds of the invention, to intermediates for their preparation, to pharmaceutical compositions comprising a compound of the invention, to the use of a compound of the invention as therapeutic agents, and to methods for the treatment of diseases and/or conditions associated with the elevated catabolism of tryptophan by administering a compound of the invention.

BACKGROUND OF THE INVENTION

[0003] The immune system can recognise cancerous cells and to stop or control their development by a long-term process known as immunosurveillance. However, during the progression to malignancy, cancer cells acquire key capabilities to aid their survival. These capabilities are referred to as the hallmarks of cancer; one of these is the ability of malignant cells to avoid destruction by the immune system (Hanahan & Weinberg, 2011). This means that in many cancers, malignant progression is accompanied by profound immunosuppression that interferes with an effective anti-tumour response and tumour elimination. The principle of immuno-oncology and immuno-therapeutics is to stimulate the patient's own immune system to generate or augment an anti-tumour immune response in order to counteract this immunosuppression and ultimately control or eradicate the cancerous cells.

[0004] Tryptophan (Trp) is an essential amino acid that must be obtained through the diet as it cannot be synthesised within the body. It is required for the biosynthesis of proteins, niacin and the neurotransmitter 5-hydroxytryptamine (serotonin). This essential nature of Trp means that any disruption to its metabolism will have a profound effect on the physiological role that it fulfils. The kynurenine pathway is responsible for the metabolism of approximately 95% of all mammalian dietary tryptophan (Adams et al., 2012).

[0005] The first and rate-limiting step in this pathway is the conversion of Trp to N-formyl kynurenine. This reaction is performed by the haem-containing enzymes indoleamine 2, 3-dioxygenase (IDO) and tryptophan 2, 3-dioxygenase (TDO) (Adams et al., 2012).

[0006] IDO has a ubiquitous pattern of expression and is also able to metabolise various Trp derivatives (Ball et al., 2014). Conversely, TDO is located primarily in the liver and is highly specific for the substrate tryptophan (Ball et al., 2014). There are two paralogs of IDO (IDO1 and ID02) which share significant identity at the amino acid level (43% for human and mouse proteins), but are structurally unrelated to the TDO protein (Ball et al., 2009).

[0007] In healthy humans, the activity of IDO and TDO remains low, exerting few physiological effects. However, under pathological conditions including allergic inflammation and infection, IDO and TDO become overexpressed. Overexpression of IDO occurs in response to inflammatory cytokines, the most potent inducer being interferon-γ (IFN-γ) which switches on gene expression and activity (Werner-Felmayer et al., 1990), whilst TDO becomes overexpressed in response to tryptophan and metabolic steroids (Sainio, 1997). It is speculated the overexpression of these key Trp metabolising enzymes serves to deplete the local supply of tryptophan to pathogens, arresting the growth of Trp-dependent intracellular pathogens such as *Toxoplasma gondii* and *Chlamydia trachomatis*.

[0008] IDO is believed to play a role in the immunosuppressive processes that prevent foetal rejection in utero. During pregnancy, the genetically disparate mammalian conceptus survives despite what would be predicted by tissue transplantation immunology. IDO expression at the maternal-foetal interface increases tryptophan catabolism, the mammalian conceptus appears to suppresses T-cell activity and defends itself against rejection.

[0009] Upregulated Trp metabolism has also been identified as a key mechanism used by cancer cells to avoid immune recognition. Many cancer cells are found to overexpress IDO and TDO. Ultimately, this overexpression leads to increased Trp metabolism and depletion in the tumour microenvironment which acts to maintain the immunosuppressive capabilities of the tumour environment by two distinct methods; Firstly, the decrease in available Trp directly inhibits activation and proliferation of effector T cells (Munn et al., 2005). T cells are extremely sensitive to tryptophan shortage and stop proliferating under such conditions. T cell cycle arrest is initiated when uncharged tRNAs detect low Trp concentrations (below 0.5-1 μM) and activate the stress kinase General Control Non-Derepressible 2 (GCN2). This initiates an amino acid starvation response which blocks the cell cycle in the G1 phase resulting in cell cycle arrest and cell death (Munn et al., 1999). Secondly, the metabolism of Trp also indirectly impacts on T cells by causing the accumulation of Trp metabolites such as 3-hydroxyanthranilic acid and quinolinic acid which act to promote the differentiation of regulatory T cells. Regulatory T cells function to supress effector T cell induction and proliferation, thereby further impacting the ability of the immune system to mount a response against the tumour (Munn et al., 1999; Fallarino et al., 2006; Mezrich et al., 2010). There is also evidence that these metabolites can directly induce T cell apoptosis (Terness et al., 2002; Fallarino et al., 2002). Combined, these mechanisms mean that T Cells are unable to launch an effective immune response in the tumour microenvironment, thus favouring tumour progression.

[0010] Moreover, Trp depletion is involved in induction of immune tolerance more generally. Accelerated Trp catabolism has been observed in diseases and disorders associated with cellular immune activation, such as infection, autoimmune diseases and AIDS, as well as during malignancy. For example, increased levels of IFNs and elevated levels of urinary Trp metabolites have been observed in autoimmune diseases; it has been postulated that systemic or local depletion of Trp occurring in autoimmune diseases may relate to the degeneration and wasting symptoms of these diseases. In support of this hypothesis, high levels of IDO were observed in cells isolated from the synovia of arthritic joints. IFNs are also elevated in human immunodeficiency virus (HIV) patients and increasing IFN levels are associated with a worsening prognosis. Thus, it was proposed that IDO is induced chronically by HIV infection, and is further